Remarks

This is in response to the final Office Action mailed April 22, 2002, and the Advisory Action mailed August 8, 2002. Claims 82-150 have been canceled and new claims 151-210 have been added. The new claims are supported in the specification and claims as originally filed. No new matter has been added.

Previous Rejections under 35 U.S.C. §103(a)

All of the previous claims were rejected as unpatentable over Bergman (US Pat. 5,501,955) in view of May et al. (US Pat. 5,622,871), with Janeway et al., Foster et al. (US Pat. 4,444,879), and Bergmann et al. (WO 95/06258) added to the rejections of specific dependent claims and the kit claims. Applicants respectfully traverse the rejections to the extent that they may be applied to the new claims.

Bergman states that a number of difficulties, some of them considerable, are often encountered with performing immunoassays for autoantibodies. The difficulties result from the autoantibody concentrations present in samples and from the nature of autoantibodies (see column 2, lines 24-28). Bergman overcame these difficulties with a test tube immunoassay for screening for autoantibodies to TPO. Modifications of the test tube conditions as described in Bergman have to date included, for example, immunofluorescence techniques; particle agglutination inhibition assays using a variety of particles; ELISA using anti-human IgG peroxidase or similar conjugate; sandwich assays using TPO coated tubes and protein A or anti-human IgG labeled with 125I or non-isotopic material; immunoprecipitation assays in which complexes of TPO autoantibodies and 125I-labelled TPO are precipitated by addition of solid phase protein A (magnetic or non-magnetic) or anti-human IgG; inhibition assays employing TPO monoclonal antibody coated tubes and TPO labeled with 125I or with non-isotopic material; and bridging assays in which the divalent nature of TPO autoantibodies is used to link liquid phase labeled (isotopically labeled or non-isotopically labeled) TPO to TPO immobilized on a solid support. Considerable research has, therefore, been carried out into optimization or modification of known techniques for use in immunoassays for autoantibodies of the type described in Bergman. However, in all of this research there

has been no teaching or suggestion of modifying any of the known assay formats to a capillary device of the type described in May et al. Additionally, Bergman describes possible variations of the assay (the different embodiments of the invention described with reference to Figures 1, 2 and 3) and discusses various reaction conditions and reagents for use in the test tube assays. However, there is nothing in the disclosure of Bergman that suggests using a capillary test device of the type taught by May et al. for detecting autoantibodies.

May et al. relate to a capillary immunoassay testing device, where antibodies are employed as specific binding reagents for an analyte antigen. May et al. provide no enabling teaching as to how such a capillary immunoassay test device might be modified to screen for ~~autoantibo~~dies rather than antigens. Indeed, although antibodies are discussed extensively in the specification of May et al., any enabling disclosure in this respect is solely in the context of reagent not analyte. Furthermore, capillary test devices of the type described in May et al. have been known for a number of years. Modifications and optimization of such capillary devices have been carried out during that time, for example in terms of substrate materials and test reagents. To the Applicant's knowledge, however, there was at the priority date of the instant application no published literature, and furthermore there still has been no published literature, that suggests or might be considered to suggest an assay method as defined in the instant claims. Applicants submit it is only with the knowledge of the present invention that such modifications might be considered.

The instant invention is directed to a method and kit for screening for autoantibodies based on a competitive screening assay in which the antigen is competing with analyte autoantibodies for interaction with either an immobilized antibody or a non-immobilized antibody. The antigen functions as a mobile binding agent that can interact with the analyte autoantibodies. In May et al., for competitive assays, the mobile labeled reagent binds to the immobilized reagent and not to the analyte. More particularly, the competition as taught by May et al. involves the labeled reagent being either the analyte itself or an analyte analogue conjugated with a label. In other words, the labeled analyte or analyte analogue migrates through the porous solid phase material into the second zone and binds the immobilized reagent. Any analyte present in the sample will compete

with the labeled reagent which will result in a reduction in the amount of labeled reagent binding in the second zone.

If one of skill in the art were to use the teaching of May et al. to provide a competitive assay for screening for autoantibodies, without knowledge of the present invention, Applicants submit the skilled artisan might immobilize an antigen on the strip and might use a mobile monoclonal autoantibody as the mobile labeled reagent, as taught by May et al. Competition would then be in terms of the autoantibody binding to the immobilized antigen but not to the mobile reagent (monoclonal). Therefore, even if the competitive techniques of May et al. were applied and modified for use in the detection of autoantibodies as has been suggested by the Examiner, one does not arrive at the instant invention where a mobile binding agent differing in nature from the analyte autoantibodies (i.e. the antigen in the instant test kit) is employed. In particular, there is no suggestion in May et al. that the competitive assays taught therein should be modified to employ three binding reagents as employed in the instant test strip and method, namely the mobile antigen, an immobilized antibody and a non-immobilized antibody.

The above distinguishing features of the instant test strip and method provide advantages in providing a sensitive test assay that is particularly advantageous for use at the point of patient care. More particularly, in the instant test strip, autoantibodies present in the sample initially bind to the antigen and are subsequently prevented from binding to immobilized and / or non-immobilized antibodies. This results in a more sensitive assay than an assay where the autoantibody and a mobile monoclonal might compete for binding to an immobilized antigen as might have been prepared based on the teaching of May et al.

Additionally, new claims 166 and 180 (corresponding to previous claims 95 and 127) require a substrate having an application zone containing antigen that is upstream of a region of immobilized antibody, with the antigen being capable of binding both the immobilized antibody and the autoantibody to be detected. None of the cited references teach or suggest a method involving the claimed substrate. Bergman teaches an assay performed in a test tube, and May et al. teach an assay involving a porous carrier. Bergman teaches embodiments where test tube assays are employed to detect autoantibodies to TPO, where a sample to be investigated is contacted with two

monoclonal antibodies and an antigen, namely TPO. The monoclonal antibodies comprise an immobilized antibody and a freely labeled antibody against the antigen. Applicants submit that if the Examiner were to consider in detail the interaction of the above referred to monoclonal antibodies, antigen and autoantibodies as described in Bergman, the Examiner would appreciate that if the antigen were to be immobilized to a substrate, such as the coated test tubes described in Bergman, detection of autoantibodies would not be possible whilst employing the remaining techniques taught by Bergman. It would, therefore be completely contrary to the teaching of Bergman to provide an antigen on an application zone of a substrate as is now defined in the claims.

Furthermore, May et al. teach an embodiment in which the porous carrier has immobilized antibodies and a labeled free reagent, but the labeled free reagent and immobilized antibody both bind the analyte. The instant invention is distinguished because the antigen initially provided on the substrate can either bind autoantibodies to be detected in the sample or the immobilized antibody. There is no motivation or guidance in the prior art for performing a method as instantly claimed.

New independent claim 168, and dependent claim 153, are directed to an assay for two different autoantibodies using a single antigen with two distinct binding sites, one to each of the two autoantibodies to be measured. The single antigen serves as a specific binding reagent for detecting two different autoantibodies. None of the cited references teach or suggest such an assay. Bergman teaches a test tube assay for detecting a single autoantibody. May et al. teach a capillary assay that can be used for detecting multiple analytes, but specifically teach using "different specific binding agents" to provide the multi-analyte test (see column 6, lines 10-12). Thus, there is no motivation or guidance for one of ordinary skill in the art to have modified the assay of Bergman to achieve the instantly claimed method.

Janeway et al. was relied upon for teaching multivalent antigens and antibody binding, and monoclonal antibody production. The Examiner asserted that, while Bergman and May et al. admittedly do not teach the detection of two autoantibodies in the same assay, it would have been obvious to modify the methods of Bergman and May et al. to include multivalent antigen and monoclonal antibodies specific for the pertinent

epitopes, as taught by Janeway et al., to achieve a selective and sensitive assay for dual analyte detection. Applicants respectfully traverse the rejection.

As stated in previous arguments, Bergman and May et al. are directed to different assay formats (test tube and capillary test strip, respectively) for the detection of single analytes. The only motivation and guidance for one of ordinary skill in the art to modify the assay of Bergman to achieve the instantly claimed assay is found in Applicants' disclosure. The Examiner has not provided a teaching or reasoning (other than that found in the instant specification) in support of the assertion that one would have been motivated to modify the assay of Bergman according to May et al. and Janeway et al. to achieve an assay for detecting at least first and second autoantibodies. Additionally, Applicants submit that even if one were to attempt such modification of Bergman, there is no reasonable expectation of success in achieving a functional and useful assay. Upon reading Bergman, May et al. and Janeway et al., one of ordinary skill in the art would know how to perform a test tube assay for autoantibodies, perform a test strip assay for analytes such as hCG, and make monoclonal antibodies against multivalent antigens. However, one would not have a reasonable expectation of success in performing the assay instantly claimed.

New claim 198 corresponds to previous claim 142, which was rejected as obvious over Bergman in view of May et al. and further in view of Foster et al. Foster et al. was relied upon for teaching an immunoassay kit containing various reagents for performing an immunoassay. The Examiner asserted that it would have been obvious to incorporate the reagents of Bergman and May et al. into a kit, as taught by Foster et al., because kits are well known in the art and widely recognized for their advantages of economy and convenience. Applicants respectfully traverse the rejection.

None of Bergman, May et al, or Foster et al. teaches or suggests a kit containing the specific reagents required in the claims. Additionally, none of the cited references provide the motivation or guidance for performing an assay utilizing the claimed reagents, as stated above. Therefore, one would not have been motivated to combine the specific reagents required by the claims into a kit.

Conclusion

In view of the amendments and comments presented herein, favorable reconsideration is respectfully requested.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903
612.332.5300

Date: 10/22/02

John J. Gresens
Reg. No. 33,112

Nancy J. Parsons
Reg. No. 40,364
JJG/NJP